UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/533,084 | 12/05/2005 | Christine Vauthier | BJS-5006-5 | 9469 |

23117 7590 06/23/2008

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

| EXAMINER | |
|---|---|
| HILL, KEVIN KAI | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/23/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/533,084 | VAUTHIER ET AL. | |
| | Examiner | Art Unit | |
| | KEVIN K. HILL | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7,11-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-10,15,16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Detailed Action

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on February 12, 2008 and April 15, 2008 have been entered.

### *Election/Restrictions*

Applicant had elected with traverse the invention of Group I, Claims 1-10, drawn to a compound comprising a hemoprotein associated with a sequenced block copolymer comprising a hydrophilic segment that is an oligosaccharide or a polysaccharide linked to at least one hydrophobic segment of Formula I and a method of using said compound as a human or animal blood substitute.

Within Group I, Applicant has elected:

i) the "X" moiety species to be CN, as recited in Claims 1 and 4;

ii) the "Y" moiety species to be of the formula "COOR-prime", as recited in Claim 1.

iii) the hemoprotein species "i", wherein the hemoprotein is a "normal hemoprotein" as recited in Claim 2, and

iv) the hydrophilic segment species "ix", wherein the hydrophilic segment is heparin, as recited in Claim 6.

### *Amendments*

In the reply filed April 15, 2008, Applicant has withdrawn Claims 7 and 11-13, amended Claims 1, 3 and 6.

Claims 7, 11-14 and 17-18 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-6, 8-10, 15-16 and 19 are under consideration.

## *Priority*

Acknowledgement is made of the certified translation, filed on April 17, 2007, of the French patent FR 02/11518 filed on September 17, 2002.

Accordingly, the effective priority date of the instant application is granted as September 17, 2002.

An updated Bib Data Sheet is provided with this Office Action, as per Applicant's request.

## *Information Disclosure Statement*

In the reply filed February 12, 2008, Applicant advances "As the WO 02/39979 version of Chauvierre is in French, and correspondence with the USPTO is to be conducted in English, the Examiner is requested in the future to refer to U.S. Patent Publication No. 2004/0028635 Al, which is believed to be equivalent to WO 02/39979 and is printed in English. Return of an initialed copy of the attached PTO 1449 Form, pursuant to MPEP § 609, which lists U.S. Patent Publication No. 2004/0028635 A1 is requested as acknowledgement of the Examiner's consideration of the reference."

The Examiner is unable to find the referenced PTO1449 Form referring to U.S. 2004/0028635 A1 in the papers filed February 12, 2008. However, in the interest of compact prosecution, the Examiner acknowledges and has considered U.S. Patent Publication No. 2004/0028635 Al. The disclosure of Chauvierre et al (WO 02/39979) will be discussed (see below) using the annotation of the disclosure of Chauvierre et al (U.S. 2004/0028635 Al).

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

1. **Claim 3 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The terms "bridged", "mutated" and "comprising peptide chains" in Claim 3 are

relative terms which render the claim indefinite. The "bridged", "mutated" and "comprising peptide chains" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

With respect to the term "bridged", the structural nature of the "bridge" and the composition to which hemoglobin is "bridged" is not disclosed, and thus the metes and bounds of the "bridged hemoglobin" is unclear.

With respect to the term "mutated", the claims embrace an enormous genus of structurally distinct hemoglobins, and thus no reference hemoglobin is provided from which the artisan would know what amino acid sequence is considered "mutated" or not "mutated", and thus the metes and bounds of the "mutated hemoglobin" is unclear..

With respect to the phrase "comprising peptide chains", those of ordinary skill in the art recognize that hemoglobin comprises heme and a protein, thus, hemoglobin inherently possesses peptide chains. Furthermore, hemoglobin exists in polymeric forms, e.g. dimers and tetramers. Thus, the structural identity and metes and bounds of the "hemoglobin comprising peptide chains" is unclear.

For the purposes of compact prosecution, the Examiner interprets the term "bridged hemoglobin" to be synonymous with "crosslinked hemoglobin", and the terms "mutated" and "comprising peptide chains" to be synonymous with "recombinant hemoglobin".

Appropriate correction and/or clarification is required.

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. **Claims 1-6, 8-10, 15-16 and 19 stand rejected under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al (WO 02/39979 A1; *of record, U.S. equivalent is 2004/0028635) and Desai et al (U. S. Patent No. 6,096,331; *of record).

The prior stated rejection has been modified slightly to reflect the amendments to the instant claim limitations.

***Determining the scope and contents of the prior art.***

Chauvierre et al teach the synthesis of nanoparticles of 1nm to 1mm [0045-46] comprising a core portion and a surface portion forming a sequenced block copolymer, said core portion comprising at least one hydrophobic segment having the formula as taught in Formula I, wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) [0010-0019], [0039] [0043-44] conjugated to a saccharide hydrophilic that may be heparin [0028]. Chauvierre et al teach that the inventive delivery system(s) may be used to administer a therapeutic agent to an animal or patient [0049-50].

Chauvierre et al do not teach the use of the heparin-coated poly(cyanoacrylate) nanoparticle for the delivery of hemoproteins such as hemoglobin. However, at the time of the invention, Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (col. 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (col. 9, lines 42-49). Desai et al do not explicitly disclose heparin as a specifically contemplated polysaccharide; however, absent evidence to the contrary, the art recognizes that heparin is a polysaccharide. Desai et al also contemplate that hemoglobin would be associated with the polymeric shell (col. 9, line 54; col. 11, line 63), thereby providing a blood substitute.

Desai et al do not disclose whether the hemoglobin is covalently or non-covalently associated with the polysaccharide shell. Rather, covalent bonding is optional (col. 11, lines 19-20).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in synthesizing nanoparticles and artificial blood substitutes for therapeutic purposes. Therefore, the level of ordinary skill in this art is high.

Neither Chauvierre et al nor Desai et al disclose the hemoglobin composition to be "gas-associated". However, the instant claims do not recite the minimum amount of gas necessary to be associated with the composition. Absent evidence to the contrary, the hemoglobin composition will inherently possess at least one gas molecule, as there is no evidence to demonstrate that the composition is "gas-free". Furthermore, given that Desai et al contemplate the use of a hemoglobin-containing nanoparticle for use as a blood substitute, one of ordinary skill in the art would reasonably expect said composition to be "gas-associated".

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to modify the nanoparticle of Chauvierre et al to include a hemoprotein such as hemoglobin as taught by Desai et al with a reasonable chance of success because Desai et al teach that the biocompatible agent, that is, hemoglobin may be associated with the nanoparticle shell comprising a polysaccharide so as to be useful as a blood substitute, and the art that has long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a* of record). An artisan would have been motivated to add hemoglobin to the nanoparticle of Chauvierre et al because the heparin moiety, well known in the art to act as an anti-coagulant as well as to inhibit complement activation, already tailors the nanoparticle for increased circulating half-life of the nanoparticle, and thus would provide an artisan with the desired delivery vehicle for a blood substitute.

Thus, the invention as a whole is *prima facie* obvious.

***Applicant's Arguments***

Applicant argues that:

a) The nanoparticles of the invention include therefore a sequenced block polymer with a particle core comprising the hydrophobic segment of formula (I), and the heparin saccharide hydrophilic segment at the surface of the particle, which is in turn associated with hemoglobin at the surface of the particle. There is no suggestion in Chauvierre or Desai to have made the claimed invention (pg 9, ¶3-4). The nanoparticles of Chauvierre et al are biologically active because the biologically active materials are IN the nanoparticle, wherein Chauvierre et al do not disclose hemoglobin as a species of said biologically active materials (pgs 9-10, joining ¶s). Chauvierre describes modification of the polysaccharide surface of the nanoparticles by "chemical functionalization" to covalently attach "ligands, such as targeting agents, labels or, more generally any compound capable of conferring on said particles a capability of reacting with an external species, such as, for example, a functional group on a support or a biological entity present in a medium under consideration" to functional groups present "on the backbone of

saccharide nature". The hemoprotein of the presently claimed invention is not a ligand described by Chauvierre (i.e., a ligand for targeting or labeling or reacting with a support) as being covalently attached to the polysaccharide surface of the nanoparticles.

b) Desai is similar to Chauvierre to the extent they teach targeted delivery of a drug or active into organs or tissues. The claimed products are not designed to target organs or tissues. The claimed invention would be contrary to the aim and teaching of both Desai and Chauvierre in this regard (pg 11).

c) The cited Desai patent fails to describe "the ultrasonic irradiation process described above" or further describe how hemoglobin is to "participate in the delivery of a biologic". Discussion follows regarding how the polymeric shell is formed and contemplated means to associate with hemoglobin as per the disclosure of Desai and references incorporated therein. (pgs 12-18) It is unclear to the Applicants what combination one of ordinary skill would have made of the teachings of Chauvierre and Desai in the absence of the present disclosure as the cited disclosures are believed to be two distinct means of making nanoparticles for delivery of encapsulated biologically active materials. The presently claimed invention however includes an active material (i.e., hemoprotein such as hemoglobin) to be associated with the surface of the core-shell nanoparticle of the claimed invention (pg 19, ¶2).

d) Grinstaff (which is incorporated-by-reference in Desai) teaches that non-crosslinked and inadequately crosslinked and prior teachings of crosslinked hemoglobin have proved unacceptable as blood substitutes (pgs 19-20, joining ¶).

e) The Applicants note the Examiner's statement that: "Desai et al disclose that hemoglobin may be present in the polymeric shell of a heparin-coated particle, thereby providing a blood substitute." See Advisory Action dated November 23, 2007. The Examiner is requested to specifically indicate where Desai provides such a teaching. A word search of the electronic copy of Desai and Grinstaff available through the USPTO web site fails to indicate where either patent teach "heparin" (pg 20, ¶2; pg 22, ¶3).

f) Applicant remarks that “The Examiner asserts, presumably as an alleged justification for a reasonable expectation of success in making the claimed invention from the combination of Chauvierre and Desai, that "the art has long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin." See Advisory Action dated November 23,

2007. The relevance of the statement is unclear. The cited art fails to teach or suggest a combination of a particle polymeric shell containing heparin which is associated with hemoglobin, as required by an embodiment of the presently claimed invention. Clarification is requested in the event the rejection of the claims over Chauvierre and Desai is maintained." (pg 22, ¶1).

g) Applicants maintain, with due respect, that the Examiner has included, in the hindsight application of the cited art, knowledge "gleaned only from the Applicant's disclosure". "As noted above however, each of the cited references describes polymeric particles for delivering encapsulated active agents.

h) The effect of altering the structure of Chauvierre was unpredictable from the cited art. (pg 24) "[w]hen free radical polymerization is used, sequenced copolymers are obtained that associate into nanoparticles where the polysaccharide chains are arranged as a brush at the nanoparticle surface. It is this "brush-like" structure that confers to the nanoparticles the long circulating life that is essential for their application as blood substitutes. There was no reasonable or predictable expectation of success from the cited references, or from the general knowledge in the art, that the surface properties of the nanoparticles, in particular their long- circulating life in blood, would not be negatively impacted if they were associated with hemoglobin. (pg 25, ¶1)

i) Applicant argues that there was no reasonable or predictable expectation of success that the hydrodynamic radius of these nanoparticles would not be negatively affected by association of hemoglobin at their surface. (pg 25)

j) Applicants submit that the quantities of hemoglobin associated at the surface of the nanoparticle may vary greatly depending on the nature of the polysaccharide present at the surface of the nanoparticle and/or depending on whether the copolymer is branched ("loop like" structure) or sequenced ("brush-like" structure). (pg 26)

Applicant's argument has been fully considered, but is not persuasive.

With respect to a), Chauvierre et al teach the instantly claimed nanoparticles comprising a hydrophobic core segment and a hydrophilic surface segment, wherein the hydrophilic saccharide that may be heparin at the surface of the particle. Desai et al taught that hemoglobin may be associated with polysaccharide-coated nanoparticles to be useful as a blood substitute. At

the time of filing of the instant application, those of ordinary skill in the art had long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a* of record). Thus, it is well within the ordinary artisans' ability to take the heparin-coated nanoparticles of Chauvierre et al and associate it with hemoglobin so as to form a product useful as a blood substitute. The means of association may be covalent or non-covalent (Desai et al, col. 11, lines 19-20). The Examiner notes that the instant specification discloses that the instantly claimed nanoparticles may further comprise additional biological agents IN the nanoparticle (pg 4, lines 25-27).

With respect to b), as a first matter, the term "tissue" has long been recognized in the art to mean "a group of similar cells performing a specific function" Source: Noland, George B. 1983. General Biology, 11th Edition. St. Louis, MO. (http://en.mimi.hu/biology/tissue.html; last visited March 12, 2008). See also "blood (tissue) Concept definition: A fluid connective tissue consisting of the plasma and cells that circulate in the blood vessels." (http://www.eionet.europa.eu/gemet/concept?cp=935, last visited March 12, 2008) Thus, blood has long been recognized by the ordinary artisan as a biological tissue.

As a second matter, the Examiner notes that the instant specification discloses that the instantly claimed nanoparticles may further comprise additional biological agents IN the nanoparticle (pg 4, lines 25-27). The instant specification also discloses the claimed product may be used as in anti-tumor therapy (pg 5, line 31). Thus, the intended use of the nanoparticles of Chauvierre et al, Desai et al and the instant product reasonably embrace each other such that Chauvierre et al and Desai et al are considered to be relevant prior art and not contrary to the claimed invention.

With respect to c), the substantive issue is that at the time of filing of the instant application, those of ordinary skill in the art possessed the conceptual knowledge that:

i) polysaccharide-coated nanoparticles associated with hemoglobin may be used as a blood substitute (e.g. Desai et al),

ii) nanoparticles of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide were known in the art (Applicant's admission, pg 19, ¶1), and

iii) heparin has a high affinity for basic proteins like hemoglobin.

Thus, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The ordinary artisan need not be limited to the means by which hemoglobin is attached to a polymeric shell as disclosed by the references incorporated within Desai. The Examiner further notes that the claimed product is NOT limited to "an active material (i.e., hemoprotein such as hemoglobin) to be associated with the surface of the core-shell nanoparticle". The instantly claimed nanoparticles may further comprise additional biological agents IN the nanoparticle (pg 4, lines 25-27).

With respect to d), Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., the means by which hemoglobin is associated with the heparin polysaccharide) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With respect to e), The Examiner responds by excerpting the relevant portion from the instant rejection: "Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (column 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (column 9, lines 42-49). Desai et al do not explicitly disclose heparin as a contemplated polysaccharide; however, absent evidence to the contrary, the art recognizes that heparin is a polysaccharide. Desai et al also contemplate that hemoglobin would be present in the polymeric shell (column 9, line 54; column 11, line 63), thereby providing a blood substitute." Thus, it would be understood by the ordinary artisan upon reading Desai et al that hemoglobin may be present in the polymeric shell of a heparin-coated particle, thereby providing a blood substitute.

With respect to f), The Examiner responds by reminding Applicant that at the time of filing of the instant application, those of ordinary skill in the art possessed the conceptual knowledge that:

i) polysaccharide-coated nanoparticles associated with hemoglobin may be used as a blood substitute (e.g. Desai et al),

ii) nanoparticles of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide were known in the art (Applicant's admission, pg 19, ¶1), and

iii) heparin (Chauvierre et al; *of record) has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a* of record). Thus, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

With respect to g), Nanoparticles of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide were known in the art (Applicant's admission, pg 19, ¶1). (pg 18, Figure; boxes 1 and 2 "hydrophobic segment"---"hydrophilic segment"). The claimed nanoparticles are not limited to the exclusion of an additional encapsulated agent. Rather, the specification discloses the instantly claimed nanoparticle may encapsulate additional agents (pg 4, lines 25-27). Thus, Chauvierre et al is relevant prior art according to the breadth of the instantly claimed product. Desai et al disclose the concept and ability to associate hemoglobin to a polysaccharide coated nanoparticle (pg 18, Figure; dashed line and box 3 "hemoglobin"). Thus, the Examiner has used only the common knowledge of the ordinary artisan and teachings of the prior art at the time of filing of the instant application to arrive at the instantly claimed product.

With respect to h), Applicant sets forth a product-by-process argument. However, Applicant's argument that the references fail to show certain features of Applicant's invention, it

is noted that the features upon which Applicant relies (i.e., the "free radical polymerization" process by which the "sequenced copolymers are obtained that associate into nanoparticles where the polysaccharide chains are arranged as a brush at the nanoparticle surface") is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With respect to i), Applicant sets forth a product-by-process argument. However, Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., the hydrodynamic radius of these nanoparticles would not be negatively affected by association of hemoglobin at their surface) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With respect to j), Applicant sets forth a product-by-process argument. However, Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., the quantities of hemoglobin associated at the surface of the nanoparticle) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, the instant claims embrace an enormous genus of distinctly different oligo- or poly-saccharides, and thus it is unclear whether the advantageous quantities of hemoglobin associated at the surface of the nanoparticle argued by Applicant is a specific formulation or a general principle achieved by all oligo- and/or poly-saccharides.

3. **Claim 3 is rejected under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al (WO 02/39979 A1; *of record, U.S. equivalent is 2004/0028635) and Desai et al (U. S. Patent No. 6,096,331; *of record), as applied to claims 1-6, 8-10, 15-16 and 19 above, and in further view of Yen et al (U.S. 5,616,311) and Bonsen et al (U.S. Patent 4,001,401).

***Determining the scope and contents of the prior art.***

Neither Chauvierre et al nor Desai et al teach the hemoglobin to be a modified hemoglobin, e.g. a bridged hemoglobin, a polymerized hemoglobin, a mutated hemoglobin or a hemoglobin comprising peptide chains. However, at the time of the invention, Yen disclosed recombinant, modified and polymerized hemoglobin (col. 6, lines 33-38) for use in nanoparticle suspensions for therapeutic administration.

Neither Chauvierre et al, Desai et al nor Yen teach the use of crosslinked hemoglobin. However, at the time of the invention, Bonsen et al disclosed blood substitutes comprising modified hemoglobin, wherein the terms "polymerized" and "crosslinked" are deemed equivalents because they refer to polyhemoglobin comprising dimeric, trimeric and/or tetrameric forms of hemoglobin (col. 3, lines 39-56).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in synthesizing nanoparticles and artificial blood substitutes for therapeutic purposes. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute hemoglobin as taught by Desai et al with a modified, e.g. crosslinked, polymerized, or recombinant, hemoglobin as taught by Yen and/or Bonsen et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute hemoglobin as taught by Desai et al with a crosslinked, polymerized, or recombinant hemoglobin because those of ordinary skill in the art have long recognized that hemoglobin tetramers are rapidly broken down into dimers, wherein said dimers are rapidly excreted by the kidneys and

cause kidney toxicity; whereas, intramolecularly crosslinked, polymerized, conjugated and/or recombinant hemoglobin demonstrate improved circulation time.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

***Potential Secondary Considerations***

It is noted that an invention that utilizes elements known in the prior art can be patentable, if the inventor has assembled a particular combination that yields unexpected results.

However, the instant claims appear to recite a very broad, generic nanoparticle blood substitute formulation with no specific materials, concentrations, or method steps that would indicate the nanoparticle blood substitute is an optimal combination of known elements.

The Examiner invites the Applicant to provide evidence that the preferred embodiments and/or working examples in the instant application are optimized protocols that yield superior results. If such evidence can be provided, and if the claims are limited in scope to those elements that are demonstrated to be critical for superior performance, then such claims may be allowable.

In the absence of any evidence of criticality or unexpected results, the instant claims are obvious variations of what was already known in the prior art (see analyses in 103 rejections, above).

In conclusion, the current claims recite generic nanoparticle blood substitute. All of the components recited are obvious variants of what was known in the art at the time of filing. If the Applicant believes they have an optimized protocol specific for producing a nanoparticle blood substitute that are critical and produce unexpected results, then the Applicant is invited to provide evidence in the form of an Affadavit under CFR 1.132 demonstrating the criticality of specific method steps and the unexpected results achieved when utilizing such method steps. In the event such evidence can be provided, then the claims must be limited in scope to recite the critical elements that produced the unexpected results. New Matter must be avoided.

## *Conclusion*

4. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

*/Q. JANICE LI, M.D./*
*Primary Examiner, Art Unit 1633*